REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons which follow.

I. Introduction

Claims 1-15 are pending. Claims 1-7 have been withdrawn from consideration as non-elected subject matter.

Applicants have amended the specification to supplement patent numbers of the prior applications to which a priority is claimed, as the examiner requested. With respect to the objection to the specification, applicants have amended the specification to delete references to "Lyon & Lyon Attorney docket No." and add the corresponding U.S. patent numbers. The specification has been further revised to recite the desired cell type, endothelial cells, at page 22, line 15, which is well known in the art and is also supported by working example 5.

Claims 8, 12, 14 and 15 have been amended to incorporate formula (I) so as to define indolinone compounds recited therein. In addition, claims 8 and 12 have been amended to include a final step that relates back to the preamble. Claim 12 has been further amended to recite the step (b) for monitoring an effect upon general disease symptoms in an adjuvant arthritis model rat. Applicants have amended claims 14 and 15 to refer to the specific compounds, "one or more indolinone compounds of formula I."

II. Rejection of claims 8-15 under 35 U.S.C. §112, second paragraph

The examiner has rejected claims 8-15 as allegedly indefinite. Applicants respectfully traverse the rejection.

In rejecting claims 8-13, the examiner asserts that claims 8-13 do not recite a final process step which clearly relates back to the preamble and the recitation of "an effect" is not clear as to what effect is being monitored. Without acquiescing to the propriety of the examiner's rejection or objection, applicants have obviated the rejection

by adding a final step, step (d) for claim 8 and step (c) for claim 12, which refers back to the preamble of claim 8 or 12.

Claim 12 has been further rejected for allegedly omitting essential steps. The examiner asserts that it is not clear as to how the method steps clearly identify the indolinone compounds by simply administering the indolinone compounds and then monitoring "an effect" upon said rats.

The claimed method is generally described from page 23, line 18 to page 24, line 5 in the specification, and Example 4 shows how to determine the effects of the indolinone compounds in an adjuvant arthritis model in rats. As described in the specification, the indolinone compounds that are active in an adjuvant arthritis model in rats are determined by monitoring an effect of the compounds on rats in the adjuvant arthritis model to include general disease symptoms such as ear nodulation, tail nodulation, nose swelling, paw swelling, and ballanitis. For example, an arthritis index is calculated from these measurements as defined in Example 4 to determine the effects of the indolinone compounds.

Thus, the specification clearly describes that the indolinone compounds are identified by monitoring an effect of the compounds on general disease symptoms in an adjuvant arthritis model rat. With this in mind, claim 12 has been further amended to define the claimed method more clearly by revising step (b) to clarify that the indolinone compounds are identified based on the effects on general disease symptoms of the adjuvant arthritis model rat.

The examiner has also rejected claims 8-13 for the recitation of "an effect" alleging that it is not clearly defined as to what effect is being monitored. Definiteness of claim language must be analyzed in light of (1) the content or the particular application disclosure, (2) the teachings of the prior art, and (3) the claim interpretation that would be given by a person skilled in the art. The term, "an effect" in either claim 8 or 12 is well-defined in the specification. That is, with respect to claim 8, the specification states that the term "effect" describes a change or an absence of a change in cell phenotype or cell proliferation, a change or an absence of a change in the catalytic activity of the protein kinase, or a change or an absence of a change in an

interaction between the protein kinase and a natural binding partner. See Page 23, 1 to 11, 4-11. As to claim 12, the specification discloses that an effect on rats in the adjuvant arthritis model includes general disease symptoms including ear nodulation, tail nodulation, nose swelling, paw swelling, and ballanitis. See page 24, lines 6-9. Thus, considering the relevant disclosure explaining "an effect" recited in claim 8 or 12, applicants respectfully submit that a person skilled in the art would readily understand the term "an effect" in claim 8 or 12 with reasonable clarity and particularity.

With respect to the rejection of claims 14 and 15, without acquiescing to the propriety to the examiner's rejection, applicants have obviated the rejection by revising these claims to use the specific compounds, the compounds of formula I.

In view of the foregoing explanation together with the amendment of claims, applicants respectfully request reconsideration and withdrawal of all the rejections under §112, second paragraph.

III. Rejection of Claims 14 and 15 under 35 U.S.C. §112, first paragraph

The examiner has rejected claims 14 and 15 for the lack of written description. Applicants respectfully traverse this rejection.

In rejecting claims 14 and 15, the examiner asserts that although claims 14 and 15 require the compound identified in either claim 8 or 12, neither claim 8 nor claim 12 actually describes a compound. Therefore, the examiner concludes that the instant specification does not contain an adequate written description for the compounds identified by the method of claims 8 or 12, nor for the methods of claims 14 and 15.

As previously mentioned, claims 14 and 15 have been amended to recite the specifically defined compounds, the compounds of formula I. Accordingly, applicants respectfully submit that such an amendment renders the rejection moot, and thus withdrawal of the rejection is respectfully requested.

IV. Rejection of claims 14 and 15 under 35 U.S.C. §101

The examiner has rejected claims 14 and 15 for a statutory type double patenting over claims 15-21 of U.S. Patent No. 5,792,783 ("the '783 patent"). Applicants respectfully traverse this rejection.

The determination of the double patenting hinges upon the scope of the claims in question. *Id.* at 1280; *In re Vogel*, 422 F.2d 438, 441 (CCPA 1970). Only if the claimed inventions are identical in scope, the rejection under 35 U.S.C. §101 is proper. *Miller v. Eagle Mfg. Co.,* 151 U.S. 186, 197, S. Ct. 310 (1894); In re *Stanley*, 214 F.2d 151, 153, (CCPA 1954).

The examiner indicates that claims 14 and 15 are interpreted to use the compounds of formula I for this rejection. The examiner seems to understand that the compounds of formula I in claims 15-21 of the '783 patent are the same as ones of formula I in the instant case. Contrary to the examiner's understanding, however, the formula I in the '783 patent does not define the same scope of the compounds as formula I in the instant application. More specifically, while A of formula I in claims 14 and 15 is defined to include 4, 5, 6, 7-tetrahydroindole, formula I in the '783 patent does not encompass this group as A. Therefore, claims 14 and 15 do not claim the same scope of methods as claimed in claims 15-21 of the '783 patent. Accordingly , applicants respectfully submit that the double patenting rejection is not proper in claims 14 and 15, and thus withdrawal of the rejection is respectfully requested.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date June 27, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Marked up replacement paragraph:

Page 1, delete the second paragraph between lines 7-12 in its entirety, and substitute the following paragraph:

This application is related to and claims priority to the United States Provisional Application Serial Number 60/089,521 which was filed by Tang, *et al.* on June 16, 1998 and entitled "METHODS FOR TREATING DISEASES AND DISORDERS RELATED TO UNREGULATED ANGIOGENESIS AND/OR VASCULOGENESIS"[(Lyon & Lyon Docket No. 227/126)] which is hereby incorporated by reference herein in its entirety including any drawings.

Page 8, paragraph 1, delete in its entirety, and substitute the following paragraph:

Formulations for indolinone compounds are described in U.S. Application Serial No. 08/702,232, filed August 23, 1996 and in the corresponding International patent publication WO 96/22976. Specific examples of parenteral and oral formulations for lipophilic compounds are contained in U.S. Patent 5,610,173, issued March 11, 1997, entitled "Formulations for Lipophilic Compounds" by D. Schwartz, *et al.* and U.S. Patent Application Serial No. 09/034,374, filed March 4, 1998, entitled "Formulations for Hydrophobic Pharmaceutical Composition" by N. Shenoy, *et al.* [(Lyon & Lyon Docket No. 231/299)] and PCT Application No. PCT/US98/04134, filed March 4, 1998, entitled "Formulations for Hydrophobic Pharmaceutical Compositions" by N. Shenoy, *et al.,* which are hereby included herein by reference in their entirety, including any drawings, figures, and tables.

Page 51, paragraph 4, delete in its entirety, and substitute the following paragraph:

Indolinone compounds of the invention can be tested for their ability to activate or inhibit protein kinases in biological assays. The methods used to measure indolinone modulation of protein kinase function are described in U.S. Application Serial No.

08/702,232, filed August 23, 1996, entitled "Indolinone Combinatorial Libraries and Related Products and Methods for the Treatment of Disease" by Tang *et al.* [(Lyon & Lyon Docket No. 221/187)], incorporated herein by reference in its entirety, including any drawings. Indolinone compounds of the invention were tested for their ability to inhibit the FLK protein kinase. Further activities and methods are described in US Patent Application Serial No. 60/045,566, filed May 5, 1997, entitled "FLK Specific Indolinone Compounds and Related Products and Methods for the Treatment of Disease" by McMahon *et al.* [(Lyon & Lyon Docket No. 225/148)], and U.S. patent application Serial No. 08/915,366, filed August 20, 1997, entitled "Indolinone Combinatorial Libraries and Related Products and Methods for the Treatment of Disease" by Tang *et al.* [(Lyon & Lyon Docket No. 227/111)], both of which are hereby included herein by reference in their entirety including any figures and drawings.

Page 56, first paragraph, after the title, delete in its entirety, and substitute the following paragraph:

The methods of the invention include the administration of indolinone compounds to patients in formulations. Formulations for indolinone compounds are described in U.S. Application Serial No. 08/702,232, filed August 23, 1996 and in International patent publication No. WO 96/22976. Some indolinone compounds are insoluble in aqueous environments, so they require the addition of compounds that can be solubilize them before administration of the pharmaceutical agents to a patient. Specific formulations, methods of making and methods of use for hydrophobic indolinone compounds are described in U.S. Patent Serial No. 5,610,173 entitled "Formulations for Lipophilic Compounds" by D. Schwartz *et al.,* U.S. Patent Application Serial No. 09/034,374, entitled "Formulations for Hydrophobic Pharmaceutical Agents," filed March 4, 1998 [(Lyon & Lyon Docket No. 232/299)], and the PCT application PCT/US98/04134, of the same title, also filed March 4, 1998, all hereby incorporated by reference herein in their entirety including any drawings, figures, or tables. The components of the formulations bind to the hydrophobic regions of the pharmaceutical agents exposing the polar regions of the solubilizing components to the solvent environment. This encapsulation of the pharmaceutical agents renders them soluble in aqueous environments.

Page 22, paragraph 2, delete in its entirety, and substitute the following paragraph:

Another aspect of the invention features methods of identifying one or more indolinone compounds that inhibit growth factor-stimulated cell proliferation comprising the following steps: (a) contacting cells with one or more indolinone compounds of Formula I; (b) contacting the cells with one or more growth factors selected from the group consisting of VEGF, PDGF, and FGF; and (c) monitoring an effect upon the cells. Preferably, the growth factor is VEGF and the cells are endothelial cells, or PDGF and the cells are smooth muscle cells, or FGF and the cells are endothelial cells. Preferably, the effect is monitored colorimetrically, for example using a change in absorbance.

Marked up rewritten claims:

8. (Amended) A method of identifying one or more indolinone compounds of Formula I that inhibit growth factor-stimulated cell proliferation comprising the following steps:

(a) contacting cells with [said] one or more indolinone compounds;

(b) contacting said cells with one or more growth factors selected from the group consisting of VEGF, PDGF, and FGF; [and]

(c) monitoring an effect upon said cells; and

(d) identifying indolinone compounds of formula I that inhibit growth factor-stimulated cell proliferation.

12. (Amended) A method of identifying one or more indolinone compounds of Formula I that are active in an adjuvant arthritis model in rats comprising the following steps:

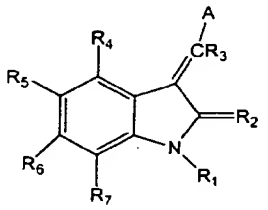
(a) administering said one or more indolinone compounds to said rats; [and]

(b) monitoring an effect upon general disease symptoms in said rats; and

(c) identifying indolinone compounds of formula I that are active in an adjuvant arthritis model in rats.

14. (Amended) A method modulating abnormal cell proliferation, modulating the activity of VEGF, FGF, or PDGF on cells *in vivo* or *in vitro* or modulating tyrosine kinase signal transduction, comprising administering to a patient in need of such treatment a pharmaceutically acceptable composition comprising a therapeutically effective amount of said one more compounds [identified by the method of either of claims 8 or 12] of formula I,

wherein said composition optionally includes one more pharmaceutically acceptable excipients in at least one of parenteral, oral, or topical formulation:

(I) 

wherein,

R_1 is H or alkyl;

R_2 is O or S;

R_3 is H;

R_4, R_5, R_6, and R_7 are each independently selected from the group consisting of hydrogen alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO_2NRR', SO_3R, SR, NO_2, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, $(CH_2)_nCO_2R$, CONRR', and $(CH_2)_nONRR'$;

A is selected from the group consisting of a 4,5,6,7-tetrahydroindole and a five-membered heteroaryl ring, wherein said five-membered ring is selected from the group consisting of thiophene, pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, isothiazole, 2-sulfonylfuran, 4-alkylfuran, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, I ,3,4-oxadiazole, I ,2,3,4,-oxatriazole, 1,2,3,5-oxatriazole, 1 ,2,3-thiadiazole, 1 ,2,4-thiadiazole, I ,2,5-thiadiazole, 1,3,4-thiadaizole, 1,2,3 ,4-thiatriazole, 1,2,3,5-thiatriazole, and tetrazole, wherein said five-membered ring

and said tetrahydroindole are optionally substituted with one or more substituents selected from the group consisting of alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO_2NRR', SO_3R, SR, NO_2, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, $(CH_2)_nCO_2R$, CONRR', and $(CH_2)_nONRR'$;

n is 0-3;

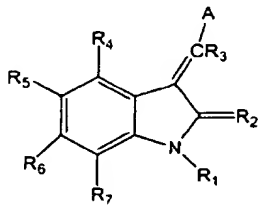
R is selected from the group consisting of H, alkyl, and aryl; and

R' is selected from the group consisting of H, alkyl, and aryl, wherein said alkyl is optionally substituted with a six-membered heteroaliphatic ring, and wherein said six-membered ring is optionally substituted at one or more positions with substituents selected from the group consisting of alkyl, alkoxy, halogen, trihalomethyl, NO_2, and $(CH_2)_nCO_2R$.

15. (Amended) A method of treating or preventing an abnormal condition by administering to a patient in need of such treatment a pharmaceutically acceptable composition comprising a therapeutically effective amount of said one or more compounds [identified by the method of either of claims 8 or 12] of formula I,

wherein said abnormal condition is selected from the group consisting of arthritis, endometriosis, ocular neovascularization, solid tumor growth and metastases, and excessive scarring during wound healing, wherein said composition optionally includes one or more pharmaceutically acceptable excipients in at least one of parenteral, oral, or topical formulation:

(I)



wherein,

R_1 is H or alkyl;

R_2 is O or S;

R_3 is H;

R_4, R_5, R_6, and R_7 are each independently selected from the group consisting of hydrogen alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO_2NRR', SO_3R, SR, NO_2, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, $(CH_2)_nCO_2R$, CONRR', and $(CH_2)_nONRR'$;

A is selected from the group consisting of a 4,5,6,7-tetrahydroindole and a five-membered heteroaryl ring, wherein said five-membered ring is selected from the group consisting of thiophene, pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, isothiazole, 2-sulfonylfuran, 4-alkylfuran, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, I ,3,4-oxadiazole, I ,2,3,4,-oxatriazole, 1,2,3,5-oxatriazole, 1 ,2,3-thiadiazole, 1 ,2,4-thiadiazole, I ,2,5-thiadiazole, 1,3,4-thiadaizole, 1,2,3 ,4-thiatriazole, 1,2,3,5-thiatriazole, and tetrazole, wherein said five-membered ring and said tetrahydroindole are optionally substituted with one or more substituents selected from the group consisting of alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO_2NRR', SO_3R, SR, NO_2, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, $(CH_2)_nCO_2R$, CONRR', and $(CH_2)_nONRR'$;

n is 0-3;

R is selected from the group consisting of H, alkyl, and aryl; and

R' is selected from the group consisting of H, alkyl, and aryl, wherein said alkyl is optionally substituted with a six-membered heteroaliphatic ring, and wherein said six-membered ring is optionally substituted at one or more positions with substituents selected from the group consisting of alkyl, alkoxy, halogen, trihalomethyl, NO_2, and $(CH_2)_nCO_2R$.